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Benton, Sally C.; Fraser, Callum George

Published in:
Annals of Clinical Biochemistry

DOI:
10.1177/0004563220967569

Publication date:
2021

Document Version
Peer reviewed version

DOI: 10.1177/0004563220967569

Annals of Clinical Biochemistry

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Journal:	*Annals of Clinical Biochemistry*
Manuscript ID	ACB-20-280
Manuscript Type:	Editorial
Date Submitted by the Author:	10-Aug-2020
Complete List of Authors:	Benton, Sally; Surrey Pathology Services, Clinical Biochemistry; Surrey Pathology Services, Bowel Cancer Screening Southern Hub Fraser, Callum; Scottish Bowel Screening Centre Laboratory,
Keywords:	Haemoglobin < Analytes, Cancer < Clinical studies, Immunoassay < Laboratory methods

Editorial

Faecal immunochemical tests in the COVID-19 pandemic; safety-netting of patients with symptoms and low faecal haemoglobin concentration – can a repeat test be used?

Sally C Benton[1] (0000-0001-9230-9088) and Callum G Fraser[2] (0000-0002-1333-7994)

[1]Clinical Biochemistry, Royal Surrey County Hospital/NHS Bowel Cancer Screening South of England Hub, Berkshire and Surrey Pathology Services, Guildford, Surrey, UK

[2]Centre for Research into Cancer Prevention and Screening, University of Dundee, Ninewells Hospital and Medical School, Dundee, Scotland, UK

Correspondence to: Sally C Benton, NHS Bowel Cancer Screening Hub, 20 Priestley Road, Surrey Research Park, Guildford, Surrey GU2 7YS, UK

E-mail: sally.benton@nhs.net

Phone: +44 (0) 1483 409850

Short title: FIT in safety-netting

Keywords: colorectal cancer, colonoscopy, COVID-19, faecal immunochemical test, faecal haemoglobin, lower bowel symptoms,

Quantitative faecal immunochemical tests for haemoglobin (FIT) are increasingly being used in the UK and elsewhere to assist in the assessment of patients presenting to primary care with lower bowel symptoms to guide referral for further investigation, often colonoscopy. A very low or undetectable faecal haemoglobin concentration (fHb) has been demonstrated in multiple studies to have a very high negative predictive value for colorectal cancer (CRC).[1]. In 2017, the National Institute for Health and Care Excellence (NICE) issued Diagnostics Guidance DG30 which encouraged the use of FIT in the assessment of patients at low risk of CRC.[2] These guidelines were then incorporated into the NICE guidance NG12 on referral of patients considered at risk of CRC.[3] DG30 advises that patients with symptoms considered low risk for CRC and with f-Hb < 10ug Hb/ g do not need to be referred on the NHS England two week wait pathway and can instead be monitored in primary care.

There are an ever-growing number of publications demonstrating the value of FIT as a rule-out investigation for CRC, in high-risk as well as low-risk symptomatic patients. particularly as a rule-out test for CRC.[4] The reason for this significant interest was that the rapidly evolving evidence was that FIT provides a simple and inexpensive test that might stem some of the ever increasing demands on scarce endoscopy services, which do not actually lead to significantly more CRC being detected.[5]

Then, the COVID-19 pandemic arrived, which led to almost complete cessation of endoscopy. This stimulated much discussion about how the many patients already referred for investigation of symptoms, and the new patients presenting with symptoms, could be provided with the best care in the challenging circumstances. Recent NHS England and NHS Improvement guidance stated: [6] Clinicians may prioritise referrals using patient-reported symptoms together with blood test results (including full blood count, FBC) and FIT. The accompanying clinical guidance stated that patients should therefore be prioritised for further investigation according to a triage process, not documented here in detail, which involved FIT. The guidance from the Scottish Government is similar and states that, when colonoscopy is either severely restricted or not available, a numerical f-Hb result and a FBC should be available whenever possible before a patient is considered for investigation of large bowel symptoms.[7] Both English and Scottish guidances have higher thresholds (f-Hb >100 µg Hb/g faeces in England; f-Hb >400 µg Hb/g faeces in Scotland) whereby patients require urgent investigations.

In both sets of guidance, patients with a f-Hb <10 µg Hb/g faeces are considered very low risk for CRC. In England, the guidance states these patients with NICE symptoms and f-Hb <10 µg Hb/g faeces should be safety-netted to a patient tracking list and, in Scotland, those with a f-Hb <10 µg Hb/g faeces should only be offered investigation where there is significant on-going clinical concern.

The guidance from England states that appropriate safety-netting should be put in place for patients who do not require immediate investigation, to allow for a further clinical assessment should their symptoms worsen. The Scottish guidance has details on use of FIT: if a patient has a FIT result <10 µg Hb/g faeces, but has persistent symptoms, a primary care review within six weeks is recommended and, if there is still doubt as to whether or not to refer, a repeat FIT may be of value. Further, in the Scottish guidance. it is documented that, in the recovery phase of COVID-19, repeating FIT in patients on the waiting list may help prioritisation.

It is well documented that FIT are not the perfect diagnostic test and, although FIT are far better than symptoms alone in the detection of CRC,[8] some cases of CRC do have f-Hb <10 µg Hb/g faeces. In consequence, for such patients, especially if their symptoms continue, safety-netting is ubiquitously recommended. Safety-netting strategies are designed so that people at low risk, but not at no risk, of having CRC are actively monitored in primary care to see if the risk of CRC changes.[9] Interestingly, as per the Scottish guidelines, recent reviews[5,10] a "best practice" guidelines paper commissioned by the Royal College of Pathologists,[11] and a recent paper,[12] all propose that repeat FIT *might* be of value, if symptoms persist, as a component of safety-netting approaches.

However, the current problem is that there is no objective evidence to support or refute the use of repeat FIT in patients with f-Hb <10 µg Hb/g faeces, who are probably at very low risk of CRC and other significant bowel diseases. Several asymptomatic population-based CRC screening programmes use two or three faecal

specimens, but these are taken from consecutive bowel motions with a view to enhancing sensitivity for the detection of CRC: lowering the f-Hb threshold achieves the same laudable aim. Some FIT-based post polypectomy screening programmes use two samples, for example, that conducted in South Australia.[13] There are only three studies, to our knowledge, that examine multiple specimen collection in the clinical setting of assessment of patients with symptoms: two have used quantitative FIT on sequential bowel motions[14,15] and one has used a qualitative FIT and three specimens.[16] However, again these replicate specimens have been collected to investigate whether sensitivity for CRC detection can be enhanced by using more than one specimen, not repeat specimens for the safety-netting of patients with f-Hb <10 µg Hb/g faeces.

There is an urgent need for research into several crucial aspects of the application of repeat FIT in patients presenting with symptoms and with f-Hb <10 µg Hb/g faeces. Necessary prerequisites to the optimum care of this large group of patients include generation of objective evidence on :

- should recommendations be developed regarding the most appropriate time interval that should elapse before a second FIT is requested: should this depend on symptom severity,
- should more than one repeat FIT be done if symptoms persist beyond the finding of two low f-Hb,

- if the repeat result is f-Hb ≥10 µg Hb/g faeces, should this be the criterion for referral for further investigation, or should a further repeat FIT be performed for confirmation of an increase in f-Hb,
- should a threshold of <10 µg Hb/g faeces be applied as the criterion for reassurance, watching and waiting, or further safety-netting, since available FIT analytical systems have detectability characteristics[17] that are below this f-Hb,[18] allowing f-Hb to be detected at very low f-Hb and quantitated at lower f-Hb than this threshold: lower thresholds do increase diagnostic sensitivity for CRC, although positivity and colonoscopy demands do increase,[19]
- should repeat or serial estimates of f-Hb in specimens from an individual patient be performed on one type of FIT system, since different systems give different numerical f-Hb results, especially at low f-Hb,[18] and
- should professional bodies provide further best practice guidelines on how the sources of pre-analytical, analytical and post-analytical variation can be minimised to ensure that any changes seen in an individual are due to important physiological or pathophysiological deterioration.

We urge all those involved in application of FIT in assessment of patients with symptoms, especially those with f-Hb <10 µg Hb/g faeces, to undertake pure or applied research, and/or report their findings to date, on repeat FIT, so that evidence can be gathered, lessons learned and best practice identified and ubiquitously translated into routine practice.

Declaration of conflicting interests

CGF undertakes paid consultancy for Hitachi Chemical Diagnostics Systems Co., Ltd, Tokyo, Japan. SCB declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Not applicable.

Guarantor

SCB

Contributorship

Both authors participated equally in the generation of this work.

ORCID iD

Sally C Benton https://orcid.org/0000-0001-9230-9088

Callum G Fraser https://orcid.org/0000-0002-1333-7994

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doi:10.1308/rcsann.2019.0144